Drug Effect of Loxofen Sodium Tablets on Pain Relief of Periodontal Endodontic Syndrome and its Influence on Inflammatory Factors

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To investigate the effect of loxofen sodium tablets on the pain relief of periodontal and pulp syndrome and its influence on the level of inflammatory factors and to investigate the medicinal value of loxofen sodium tablets and to provide reference for the treatment of periodontal and endodontic syndrome is the objective of the study. 102 patients with periodontal endodontic syndrome were randomly divided into treatment group (51 patients) and control group (51 patients). The treatment group was treated with loxofen sodium tablets, while the control group was treated with ibuprofen sustained-release capsules. After treatment, the clinical efficacy, pain score, inflammatory factors levels and adverse incidence of the two groups were recorded. The total effective rate of the treatment group was 78.43 % higher than 58.83 % of the control group ($p<0.05$). Before treatment, there were no significant differences in pain score and inflammatory factor levels between the two groups ($p>0.05$). After medication, the improvement of pain in treatment group was better than that in control group ($p<0.05$). After treatment, the level of inflammatory factors in the treatment group was lower than that in the control group ($p<0.05$). Loxofen sodium tablet is better than ibuprofen sustained-release capsule in alleviating the pain of periodontal pulp syndrome. Loxofen sodium tablets have obvious effects on improving pain and reducing the level of inflammatory factors in patients and its medication has recommended value.

Key words: Loxofen sodium tablets, ibuprofen sustained-release capsule, periodontal pulp syndrome, drug use, inflammatory cytokines

Loxofen sodium tablets were first developed and marketed in Japan during the period of July 1986. Loxofen sodium belongs to phenylpropionate non-steroidal anti-inflammatory drugs, mainly used in the clinical use of various kinds of inflammation, waist and shoulder pain and other diseases. Loxofen sodium is a precursor drug that is absorbed by the digestive tract and converted into an active metabolite in the body. This metabolite inhibits the synthesis of prostaglandins and thus acts as an anti-inflammatory, analgesic and antipyretic agent. In recent years, loxofen sodium tablets have been widely used in stomatology, especially in the treatment of pain relief of periodontal pulp syndrome. Periodontal pulp syndrome is one of the most common diseases in stomatology. It is usually divided into two categories. One is to have pulp apical periodontal disease first and periodontal disease later. The other type is to have periodontal disease first and then pulp apical lesions appear. The specific clinical manifestations are different according to the classification. This paper mainly studies the pulp apical lesions caused by the retrograde infection of periodontal disease. The clinical manifestations of the affected teeth are periodontal pockets deep into the apical area or severe gingival atrophy and alveolar bone resorption. Cold and hot stimulation can aggravate the pain and there is discomfort or pain when biting and rapping. It is generally believed that the main cause of periodontal pulp syndrome is bacterial infection. In addition to loxofen sodium tablets, ibuprofen sustained-release capsules are also widely used to relieve the pain of periodontal pulp syndrome. For two different drugs, comparative study of the total effective rate, pain improvement, inflammatory factors in the treatment of periodontal pulp and comprehensive diseases, has

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certain practical significance.

MATERIALS AND METHODS

Data information:

A total of 102 patients with periodontal and endodontic syndrome admitted to the Future City Science and Technology City of Hangzhou Stomatological Hospital from December 2021 to September 2022 were selected as the research objects. The subjects were randomly divided into treatment group and control group, with 51 patients in each group. Treatment group include 27 males and 24 females, the average age was 49.12±4.42 y (range, 40-58 y). Control group include 25 males and 26 females, the average age was 49.06±4.16 y (range, 39-59 y). There was no significant difference between the two groups ($p>0.05$). All patients were collected with the informed consent of the patients and in accordance with the hospital ethics code.

Inclusion and exclusion criteria:

Inclusion criteria: Patients meet the diagnostic criteria of periodontal endodontic syndrome; obvious pain after hot and cold stimulation; no obvious caries or defects were observed; periodontal pocket depth>5 mm, there was obvious periodontal tissue destruction; complete patient data, capable of in-depth research.

Exclusion criteria: Patients with primary endodontics; patients with simple periodontal abscess; patients with heart, liver and kidney dysfunction; patients with severe systemic diseases such as diabetes, renal failure, Acquired Immunodeficiency Syndrome (AIDS), cancer patients who have received radiotherapy and chemotherapy in the last 6 mo; pregnant or lactating patients.

Methods:

In the treatment group, all patients were given periodontal basic treatment. The methods included taking X-ray films to observe the lesion location, area size and lesion status of alveolar bone and root apical tissue. Patients were treated with general root canal therapy; the patient's periodontal pocket and other areas were rinsed with normal saline and oral loxofen sodium tablets were given. Loxofen sodium tablets are manufactured by the First Total Pharmaceutical Co., Ltd. (Shanghai), Sinopharm approval H20030769, specification: 60 mg/tablet. Take one tablet orally 3 times a day after meals. The medication period was 5 d and the patient was reexamined 5 d later.

The control group and the treatment group had the same basic method, but the oral medication was different. The control group took ibuprofen sustained-release capsules orally. Ibuprofen sustained-release capsule is produced by Sino-American Tianjin Smith Kline Pharmaceutical Co., Ltd., SINophospH10900089, specification: 0.3 g/capsule, take orally 1 time after breakfast, 1 capsule each time. The medication period was 5 d and the patient was reexamined after 5 d.

Observation indexes and criteria:

Comparison of pain scores between the two groups before and after medication: The pain score of patients: 0-3 points; comparative pain score 3-6; severe pain on a scale of 7-10. The patient was informed of the pain score criteria and the patient scored the pain at the first diagnosis and review, and recorded in the medical record.

Comparison of levels of inflammatory factors between the two groups before and after medication: Venous blood samples were collected after fasting and the general volume was 3 ml. The serum White Blood Cell (WBC) count, C-Reactive Protein (CRP), Procalcitonin (PCT), *Staphylococcus aureus*, *Porphyromonas gingivalis*, *Streptococcus mutans* and *Streptococcus pneumoniae* were detected by the laboratory department. The WBC count, CRP, PCT decreased, which indicated that there was a certain effect of medication, inflammation was alleviated. *Staphylococcus aureus*, *Porphyromonas gingivalis*, *Streptococcus mutans*, *Streptococcus pneumoniae* decreased, indicating that the pathogens were removed to a certain extent, the less inflammatory factors, better the effect of medication.

Comparison of drug effects between the two groups: After 5 d of medication, the effect of medication was judged according to the patient's recovery. The periodontal pocket of all patients was observed, the periodontal pocket depth was reduced by more than 2 mm, gingival bleeding disappeared, gingival swelling was not observed, no pain or pain was negligible and the effect was significant. If the depth of periodontal pocket is reduced by 1-2 mm, gingival bleeding occurs occasionally, gingival redness and swelling are not obvious, and pain is relieved obviously, the situation is improved. If the periodontal pocket is not improved, the gingival bleeding is not reduced, the gingival swelling is not significantly reduced and the pain is not effective. Total effective rate=Apparent

efficiency+Improvement rate.

Comparison of the incidence of adverse drug use between the two groups: If the patient's condition is reviewed after medication or the patient feels unwell after medication, it is noted that poor medication occurs. Reexamination of the patient after medication included nausea, retching, fever, hyperhidrosis and apical tissue necrosis.

Statistical methods:

Statistical Package for the Social Sciences (SPSS) 16.0 statistical software was used to process relevant data, t-test was used for comparison between observation group and control group and $p<0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Comparison of pain scores after medication was shown in Table 1. After medication, the pain score of the treatment group was lower than that of the control group. This indicates that loxofen sodium tablet is more effective than ibuprofen sustained-release capsule in the treatment of periodontal and pulp syndrome, and the comparison between the two groups is statistically significant.

Comparison of inflammatory factors before and after medication was shown in Table 2. WBC count, CRP and PCT were considered as important indicators of inflammatory factors. Through medication followed by observation, both loxofen sodium tablets and ibuprofen sustained-release capsules can reduce inflammatory factors. However, loxofen sodium tablets selected in the treatment group were more obvious in reducing inflammatory factors than ibuprofen sustained-release capsules in the control group and the comparison was statistically significant.

Pathogens are one of the manifestations of inflammatory factors. Generally, the main pathogens of periodontal pulp syndrome are *Staphylococcus aureus*, *Porphyromonas gingivalis*, *Streptococcus mutans*, *Streptococcus pneumoniae* and so on. Therefore, it is an important direction to study the number of changes in pathogenic bacteria after different drugs. Through two different drugs, loxofen sodium tablets and ibuprofen sustained-release capsules, it was found that the pathogen clearance rate of loxofen sodium tablets was 88.89 % and that of ibuprofen sustained-release capsules was 80.85 %. There is a significant difference between the two with statistical significance (Table 3).

TABLE 1: COMPARISON OF PAIN INDEX SCORES BEFORE AND AFTER MEDICATION OF DIFFERENT DRUGS IN TWO GROUPS ($\bar{x}\pm s$)

Group	Number of patients	Pain index score	
		Before medication	After medication
Treatment group	51	7.24±0.21	3.16±0.19
Control group	51	7.26±0.22	4.32±0.23
t		0.098	4.37
p		0.862	<0.05

TABLE 2: COMPARISON OF INFLAMMATORY FACTORS IN THE TWO GROUPS BEFORE AND AFTER MEDICATION ($\bar{x}\pm s$)

Group	Number of patients	WBC ($\times10^9$/l)		CRP (mg/l)		PCT (mmol/l)	
		Before medication	After medication	Before medication	After medication	Before medication	After medication
Treatment group	51	12.42±4.18	9.65±1.38	18.48±3.28	8.93±1.62	11.46±1.68	4.39±1.04
Control group	51	12.68±4.32	8.02±1.06	18.63±3.39	6.52±1.25	11.64±1.79	3.24±0.86
t		0.128	4.182	0.133	5.218	0.314	3.665
p		0.846	<0.05	0.928	<0.05	0.725	<0.05

TABLE 3: COMPARISON OF PATHOGEN CLEARANCE RATE BEFORE AND AFTER MEDICATION IN TWO GROUPS

Pathogens	Treatment group			Control group		
	Number of investigations	Number of pathogens removed	Clearance rate	Number of investigations	Number of pathogens removed	Clearance rate
Staphylococcus aureus	14	13	92.86 %	14	12	85.71 %
Porphyromonas gingivalis	12	10	83.33 %	13	9	69.23 %
Streptococcus pneumoniae	8	7	85.7 %	8	7	87.5 %
Streptococcus mutans	11	10	90.91 %	12	9	75 %
Total	45	40	88.89 %	47	38	80.85 %

Different drug effects were illustrated in Table 4. The treatment group received loxofen sodium tablets, while the control group received ibuprofen sustained-release capsules. The overall effective rate was 78.43 % in the treatment group and 58.83 % in the control group. The difference between the two groups was statistically significant as shown in Table 4.

The therapeutic effect of periodontal endodontic syndrome was refined by periodontal pocket depth, gingival bleeding, gingival redness and swelling index, and pain score. Evaluation of these indexes is helpful to judge the efficacy of different drugs. There was no significant difference between loxofen sodium tablets and ibuprofen sustained-release capsules. After treatment, the depth of periodontal pocket decreased significantly, the amount of gingival bleeding decreased, the redness and swelling improved and the pain score was lower in the loxofen sodium tablet group. The results were significant and statistically significant as shown in the Table 5.

Comparison of the incidence of maladministration of different drugs was shown in Table 6. In the treatment group, 2 patients (3.92 %) had nausea, 2 patients (3.92 %) had retching, 1 patient (1.96 %) had fever, 3 patients (5.88 %) had dry fever and 1 patient (1.96 %) had apical necrosis. In the control group, ibuprofen sustained release capsule was used and nausea occurred in 3 patients (5.88 %), retching in 2 patients (3.92 %), fever in 2 patients (3.92 %), dry and hot sweating in 4 patients (7.84 %) and apical tissue necrosis in 2 patients (3.92 %). Overall adverse events were 17.65 % in the treatment group and 25.49 % in the control group. The difference between the two groups was statistically significant as shown in the Table 6.

Loxofen sodium tablets, as a non-steroidal antipyretic and analgesic drugs, have the effects of clearing heat, analgesia, antibacterial and anti-inflammatory. As a clinical drug, loxofen sodium tablets are mainly applicable for three indications, namely the anti-inflammatory and analgesic effects of rheumatoid arthritis, osteoarthritis, cervical spondylitis and other diseases. Anti-inflammatory and analgesia after surgery or trauma or tooth extraction; heat clearing and analgesia of upper respiratory tract infection was observed. The main component of loxofen sodium tablets is loxofen sodium, with a molecular formula of $C_{15}H_{17}NaO_3.2H_2O$. Loxofen sodium tablets are pale pink in color. Studies have shown that loxofen sodium tablets can cause adverse reactions such as shock, hemolytic anemia, cutaneous and mucocutaneous eye syndrome, nephrotic syndrome, interstitial pneumonia and liver dysfunction[1]. Therefore, in clinical medication, it should be strictly implemented in accordance with the medication attention and drug interaction, rational drug use. If you feel unwell, stop the medication as soon as possible. Avoid the use of two non-steroidal drugs at the same time; it should be a single drug. Studies have also shown that loxofen sodium is a cyclooxygenase inhibitor and its pharmacology is to block the conversion between arachidonic acid and prostaglandins, thus playing anti-inflammatory and analgesic effects, and compared with other western drugs, this drug has low side effects[2].

TABLE 4: EFFICACY OF DIFFERENT DRUGS (x̄±s)

Group	Number of patients	Effective	Get better	Invalid	Total efficiency
Treatment group	51	12 (23.53 %)	28 (54.9 %)	11 (21.57 %)	78.43 %
Control group	51	9 (17.65 %)	21 (41.18 %)	21 (41.18 %)	58.83 %
Chi square (χ^2)		3.62	1.95	6.48	6.29
p		>0.05	>0.05	<0.05	<0.05

TABLE 5: COMPARISON OF PERIODONTAL STATUS BETWEEN THE TWO GROUPS AFTER DIFFERENT MEDICATIONS (x̄±s)

Group	Number of patients	Periodontal pocket depth (mm)		Bleeding index		Red swelling index		Pain score	
		Before medication	After medication	Before medication	After medication	Before medication	After medication	Before medication	After medication
Treatment group	51	6.08±1.16	4.05±1.32	4.63±0.38	2.02±0.32	4.92±0.82	2.46±0.77	7.24±0.21	3.16±0.19
Control group	51	6.11±1.08	5.22±1.29	4.64±0.35	3.38±0.33	4.93±0.83	3.25±0.78	7.26±0.22	4.32±0.23
t		0.077	4.215	0.079	6.312	0.072	6.825	0.098	4.37
p		0.932	<0.05	0.966	<0.05	0.975	<0.05	0.862	<0.05

TABLE 6: COMPARISON OF THE INCIDENCE OF MALADMINISTRATION OF DIFFERENT DRUGS [n (%)]

Group	Number of patients	Nausea	Retching	Fever	Better heat	Necrosis of the apical tissue	Total
Treatment group	51	2 (3.92)	2 (3.92)	1 (1.96)	3 (5.88)	1 (1.96)	9 (17.65)
Control group	51	3 (5.88)	2 (3.92)	2 (3.92)	4 (7.84)	2 (3.92)	13 (25.49)
χ^2		0.627	9.768	1.236	0.529	1.236	1.854
p		<0.05	0.254	<0.05	<0.05	<0.05	<0.05

After oral administration, loxofen sodium tablets enter the human gastrointestinal system, which will be absorbed in the most original form and quickly transformed into trans-hydroxyl active substances. After completing the transformation, loxofen sodium tablets will rapidly inhibit the transformation of prostaglandins and the formation of thromboxane, thereby reducing the irritation to the intestine and achieving the purpose of pain relief[3]. Prostaglandins themselves have pain-causing effects and can also increase the sensitivity of nociceptors to pain-causing molecules. Inhibition of prostaglandin conversion is a process of analgesic conversion.

Ibuprofen sustained-release capsules belong to propionic acid type non-steroidal antibacterial and anti-inflammatory drugs, and loxofen sodium tablets belong to the same type of drugs. Ibuprofen sustained-release capsules are commonly used to relieve toothache, migraines, neuralgia and menstrual cramps. It is also commonly used for fever caused by common influenza. It can be seen that the main clinical application and direction of ibuprofen sustained-release capsule is analgesia and antipyretic. Ibuprofen sustained-release capsules are mainly distributed as Loprofen and the excipients are sugar, starch, stearic acid and polyvinylpyrrolidone. Its color is white. Studies have shown that the

simultaneous use of ibuprofen sustained release capsules with other antipyretic and analgesic drugs will increase gastrointestinal adverse reactions and may lead to ulcers[4]. Therefore, ibuprofen sustained-release capsule should be used as a single analgesic and antipyretic drug in clinical use, same type of drugs are not used simultaneously. Some studies have also shown that the use of ibuprofen sustained-release capsules together with anticoagulants such as heparin and dicoumarins (such as warfarin) can cause prolonged prothrombin time and increase bleeding pour[5]. At the same time, studies have shown that when ibuprofen sustained-release capsules are used together with oral hypoglycemic drugs, the blood drug concentration is likely to be too high[6]. Therefore, patients with diabetes should avoid ibuprofen sustained-release capsules when taking medication. Ibuprofen sustained-release capsules can inhibit the synthesis of prostaglandins, which has basically the same pharmacological effect as loxofen sodium tablets. Ibuprofen sustained-release capsules are sustained-release formulations that allow the drug to be released slowly in the body. In general, a single oral dose of ibuprofen sustained-release capsules can last for 12 h. Few patient's may have nausea, vomiting, gastrointestinal burning or digestive discomfort, headache, dizziness, tinnitus, blurred vision and other adverse reactions after taking ibuprofen sustained-release capsules. Some studies have shown that a small number of patients will have rare rash, allergic nephritis, cystitis, renal failure and other adverse consequences. It is clinically found that patients with intestinal diseases, such as duodenal gastritis, who took ibuprofen sustained-release capsules, may increase their illness[7]. Patients with post-herpetic neuralgia who took ibuprofen sustained release capsule had adverse reactions 12 d after taking the drug and the main symptoms were papules, erythema, pain and itching on the extremities. He had facial edema on d 17. After 13 d of discontinuation of ibuprofen sustained-release capsules, the facial swelling disappeared and the rash on the limbs disappeared.

Periodontal pulp syndrome is one of the common diseases in stomatology. At present, there is no specific treatment for periodontal endodontic syndrome and there is no specific drug. It is generally believed that bacterial infection is the main cause of periodontal endodontic syndrome[8]. At present, there is no consensus on the molecular dysregulation mechanism of periodontal endodontic syndrome. Studies have shown that periodontal pulp syndrome is sensitive to the external environment, similar to the microbial infection caused by wisdom teeth[9]. The development of inflammatory factors will eventually be transmitted to nerve sources and cause pain. The expression of periodontal pulp syndrome in periodontal tissue is the analytical expression of inflammatory factors related to pain. The appearance of inflammatory factors in periodontal pulp syndrome may be dysregulated by genes in the progression of periodontal pulp syndrome and dysregulated genes are involved in biological functions or signaling pathways associated with immune inflammation. Studies have shown that infection caused by the combination of aerobic and anaerobic bacteria in the periodontal pocket is the main cause of periodontal pulp syndrome[10]. Therefore, the core of the treatment of periodontal endodontic syndrome is to suppress these two pathogens. Root canal therapy and periodontal therapy supplemented with drug therapy can kill and treat bacteria. The use of bactericidal, anti-inflammatory and analgesic drugs is the first choice for the treatment of periodontal pulp syndrome. The host immune response and inflammatory response are easy to destroy periodontal tissue and the abnormal occurrence of inflammatory factors is closely related to the development of pulpitis[11]. The WBC count, CRP and PCT in patients with periodontal pulp syndrome were significantly higher than those in normal subjects. The WBC count is involved in the inflammatory response of the patient's tissue, which causes pain in the patient. CRP dominates the progression of pulpitis. PCT participates in and mediates the pathological process of pulpitis.

This study found that loxofen sodium tablets and ibuprofen sustained-release capsules belong to the same type of drugs, which are used in the clinical treatment of pain relief of periodontal and pulp syndrome, but the efficacy of loxofen sodium tablets is better than that of ibuprofen sustained-release capsules. In particular, this study noted that loxofen sodium tablets were superior to ibuprofen sustained-release capsules in the elimination of pathogens. The ibuprofen sustained-release capsule product specification also indicates that its efficacy is antipyretic and analgesic. This shows that ibuprofen sustained-release capsule is still obviously insufficient in anti-inflammatory and sterilization. As mentioned above, the cause of periodontal endodontic syndrome is pathogen infection, which is preceded by pathogen and the occurrence of pathogen

leads to pain. Although ibuprofen sustained-release capsule has a good effect on analgesia, it cannot effectively eliminate pathogenic bacteria, so it cannot completely cure periodontal pulp syndrome. So this also explains that loxofen sodium tablets showed significantly less inflammatory cytokines than ibuprofen sustained-release capsules. Similarly, we also see that loxofen sodium tablets cannot eliminate all pathogens and there is still a certain lack of improvement in inflammatory factors. Therefore, in clinical use, loxofen sodium tablets as analgesic and anti-inflammatory drugs, and it is necessary to add some other simple anti-inflammatory drugs to supplement the lack of anti-inflammatory effect of loxofen sodium tablets.

In conclusion, loxofen sodium tablets have a certain clinical effect in the treatment of periodontal endodontic syndrome, which can improve the pain of patients, reduce the level of inflammatory factors in patients and the overall effective rate of patients is high. However, loxofen sodium tablets still have some shortcomings in eliminating pathogenic bacteria and reducing inflammatory factors in patients. In general, loxofen sodium tablets are recommended to relieve the pain of periodontal and pulp syndrome, but anti-inflammatory drugs can also be given.

Conflict of interests:

The authors declared no conflict of interest.

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